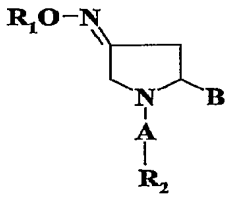
Claims

1. A method of preparing a compound according to formula (I):



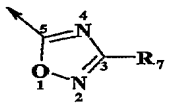
(I)

wherein

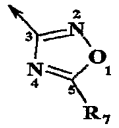
A is a carbonyl group -(C=O)-;

B is selected from the group consisting of an oxadiazole ring, an amido group of the formulae $-(C=O)-NR_3R_4$, and $-(CH_2)n-X-R_8$;

wherein the oxadiazole ring is any of the formulae:



(Xa)



(Xb)

R_1 is H or a C_1-C_6-alkyl;

R_2 is selected from the group consisting of aryl, heteroaryl and saturated or unsaturated 3-8-membered cycloalkyl;

R_3 and R_4 are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, alkoxy, sulfanyl, acyl, alkoxycarbonyl, aminocarbonyl, saturated or unsaturated 3-8-membered cycloalkyl which may contain 1 to 3 heteroatoms selected of N, O, S, aryl, heteroaryl, C_1-C_6-alkyl aryl and C_1-C_6-alkyl heteroaryl;

X is O or NR_9;

R_8 is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_1-C_6-alkyl aryl, heteroaryl, C_1-C_6-alkyl heteroaryl, C_2-C_6-alkenyl, C_2-C_6-alkenyl aryl, C_2-C_6-alkenyl heteroaryl, C_2-C_6-alkynyl, C_2-C_6-alkynyl aryl, C_2-C_6-alkynyl heteroaryl, C_3-C_8-cycloalkyl, heterocycloalkyl, C_1-C_6-alkyl cycloalkyl, C_1-C_6-alkyl heterocycloalkyl, C_1-C_6-alkyl carboxy, acyl, C_1-C_6-alkyl acyl, C_1-C_6-alkyl acyloxy, C_1-C_6-alkyl alkoxy, alkoxycarbonyl, C_1-C_6-alkyl alkoxycarbonyl, aminocarbonyl, C_1-C_6-alkyl aminocarbonyl, C_1-C_6-alkyl acylamino, C_1-C_6-alkyl ureido, amino, C_1-C_6-alkyl amino, sulfonyloxy, C_1-C_6-alkyl sulfonyloxy, sulfonyl, C_1-C_6-alkyl sulfonyl, sulfinyl, C_1-C_6-alkyl sulfinyl, C_1-C_6-alkyl sulfanyl and C_1-C_6-alkyl sulfonylamino;

R_7 is selected from the group consisting of hydrogen, sulfonyl, amino, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, wherein said alkyl, alkenyl, alkynyl chains are optionally interrupted by a heteroatom selected from N, O or S, aryl, heteroaryl, saturated or unsaturated 3-8-membered cycloalkyl, heterocycloalkyl, wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl groups are optionally fused with 1-2 further cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, an acyl moiety, C_1-C_6-alkyl aryl, C_1-C_6-alkyl heteroaryl, C_1-C_6-alkenyl aryl, C_1-C_6-alkenyl heteroaryl, C_1-C_6-alkynyl aryl, C_1-C_6-alkynyl heteroaryl, C_1-C_6-alkyl cycloalkyl, C_1-C_6-alkyl heterocycloalkyl, C_1-C_6-alkenyl cycloalkyl, C_1-C_6-alkenyl heterocycloalkyl, C_1-C_6-alkynyl cycloalkyl, C_1-C_6-alkynyl heterocycloalkyl, alkoxycarbonyl, aminocarbonyl, C_1-C_6-alkyl carboxy, C_1-C_6-alkyl acyl, C_1-C_6-alkyl acyloxy, C_1-C_6-alkyl alkoxy, C_1-C_6-alkyl alkoxy-carbonyl, C_1-C_6-alkyl aminocarbonyl, C_1-C_6-alkyl acylamino, C_1-C_6-alkyl ureido, C_1-C_6-alkyl amino, C_1-C_6-alkyl ammonium, C_1-C_6-alkyl sulfonyloxy, C_1-C_6-alkyl sulfonyl, C_1-C_6-alkyl sulfinyl, C_1-C_6-alkyl sulfanyl, C_1-C_6-alkyl sulfonylamino, C_1-C_6-alkyl aminosulfonyl, hydroxy, halogen and cyano;

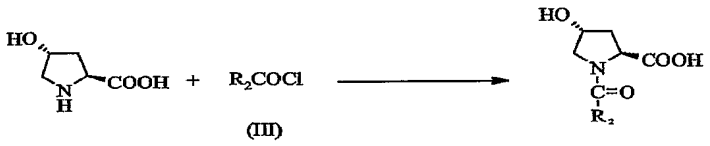
R_9 is selected from the group consisting of hydrogen, C_1-C_6-alkyl, C_1-C_6-alkyl aryl, C_1-C_6-alkyl heteroaryl, aryl and heteroaryl;

R_8 and R_9 can form together with the N atom to which they are linked to, a 5-8 membered saturated or unsaturated heterocycloalkyl ring; and

n is an integer from 1 to 3;

said method comprises the following steps :

Step 1 : transformation of the pyrrolidine of formula (II) into an acyl derivative of formula (IV) using an acylating agent (III) :



(II) (III) (IV)

Step 2 : Oxidation of the acyl derivative (IV), with a oxidizing agent, obtaining a pyrrolidone of formula (V) :

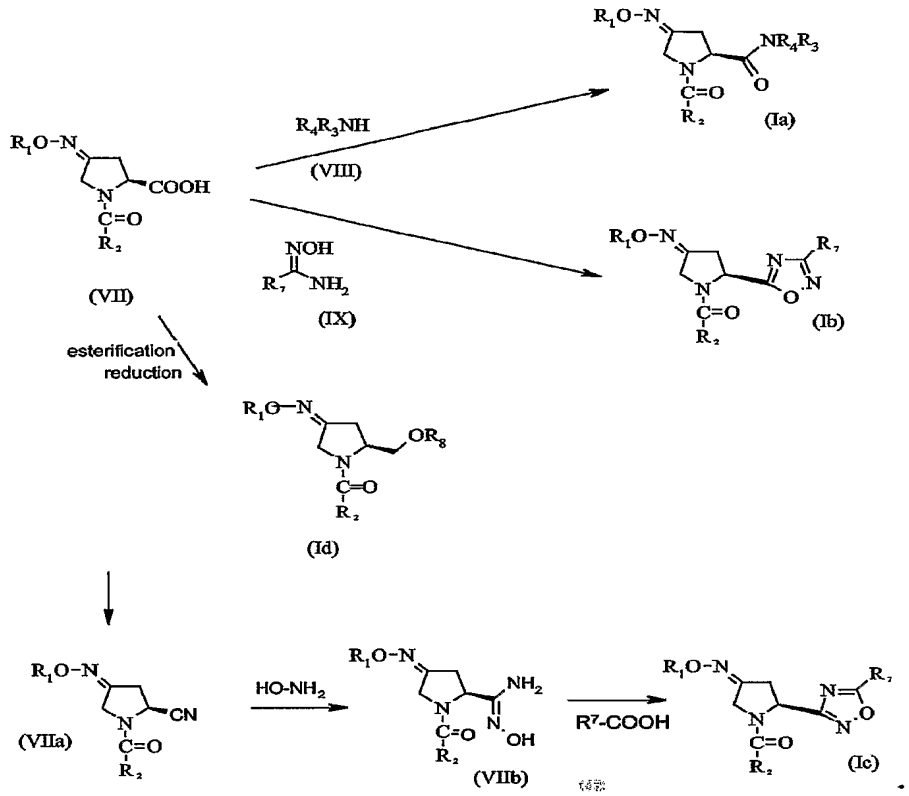
(IV) (V)

Step 3 : Transformation of the pyrrolidone of formula (V) into compound (VII) using a suitable alkoxylamine, aryloxylamine or hydroxylamine of general formula (VI) :

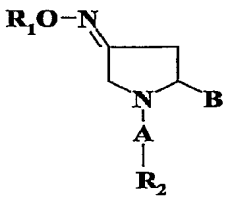
(V) (VI) (VII)

Step 4 : Transformation of the compound (VII) with an amine of general formula (VIII) or an N-hydroxyamidine of general formula (IX) thus yielding compounds (Ia) and (Ib), or transforming compound (VII) first into a nitrile (VIIa), which is then transformed into the hydroxyamidine (VIIb) that is then reacted with a carboxylic acid

R^7-COOH to yield compound (Ic), or first esterifying and than reducing compound (VII) using a suitable esterification or reducing agent, respectively, thus yielding compound (Id):



2. The method of preparing a compound according to formula (I) according to claim 1:

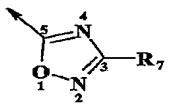


(I)

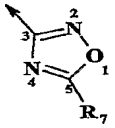
wherein

A is a carbonyl group -(C=O)-;

B is either an amido group of formula –(C=O)-NR_3R_4 or an oxadiazole ring of any of the formulae:



(Xa)



(Xb)

R_7 is selected from the group consisting of hydrogen, sulfonyl, amino, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, wherein said alkyl, alkenyl, alkynyl chains are optionally interrupted by a heteroatom selected from N, O or S, aryl, heteroaryl, saturated or unsaturated 3-8-membered cycloalkyl, heterocycloalkyl, wherein said cycloalkyl, heterocycloalkyl, aryl or heteroaryl groups are optionally fused with 1-2 further cycloalkyl, heterocycloalkyl, aryl or heteroaryl group, an acyl moiety, C_1-C_6-alkyl aryl, C_1-C_6-alkyl heteroaryl, C_1-C_6-alkenyl aryl, C_1-C_6-alkenyl heteroaryl, C_1-C_6-alkynyl aryl, C_1-C_6-alkynyl heteroaryl, C_1-C_6-alkyl cycloalkyl, C_1-C_6-alkyl heterocycloalkyl, C_1-C_6-alkenyl cycloalkyl, C_1-C_6-alkenyl heterocycloalkyl, C_1-C_6-alkynyl cycloalkyl, C_1-C_6-alkynyl heterocycloalkyl, alkoxycarbonyl, aminocarbonyl , C_1-C_6-alkyl carboxy, C_1-C_6-alkyl acyl, C_1-C_6-alkyl acyloxy, C_1-C_6-alkyl alkoxy, C_1-C_6-alkyl alkoxy-

carbonyl, C_1-C_6-alkyl aminocarbonyl, C_1-C_6-alkyl acylamino, C_1-C_6-alkyl ureido, C_1-C_6-alkyl amino, C_1-C_6-alkyl ammonium, C_1-C_6-alkyl sulfonyloxy, C_1-C_6-alkyl sulfonyl, C_1-C_6-alkyl sulfinyl, C_1-C_6-alkyl sulfanyl, C_1-C_6-alkyl sulfonylamino, C_1-C_6-alkyl aminosulfonyl, hydroxy, halogen and cyano;

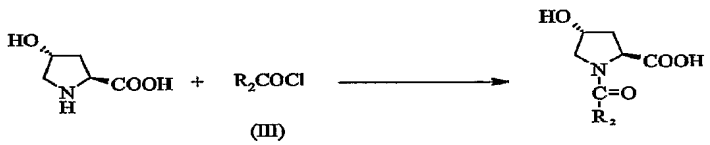
R_1 is H or a C_1-C_6-alkyl;

R_2 is selected from the group consisting of aryl, heteroaryl and saturated or unsaturated 3-8-membered cycloalkyl;

R_3 and R_4 are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, alkoxy, sulfanyl, acyl, alkoxycarbonyl, aminocarbonyl, saturated or unsaturated 3-8-membered cycloalkyl which may contain 1 to 3 heteroatoms selected of N, O, S, aryl, heteroaryl, C_1-C_6-alkyl aryl and C_1-C_6-alkyl heteroaryl;

said method comprises the following steps :

Step 1 : transformation of the pyrrolidine of formula (II) into an acyl derivative of formula (IV) using an acylating agent (III) :

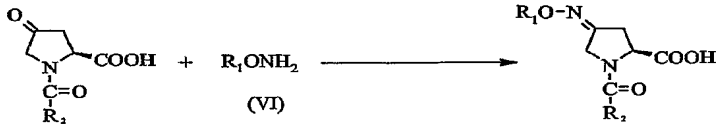


(II) (III) (IV)

Step 2 : Oxidation of the acyl derivative (IV), with a oxidizing agent, obtaining a pyrrolidone of formula (V) :

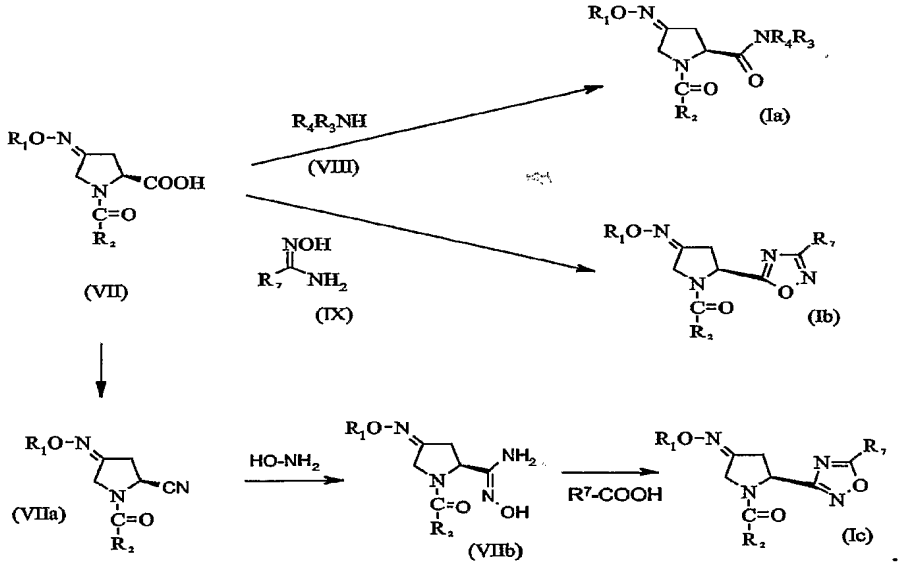
(IV) (V)

Step 3 : Transformation of the pyrrolidone of formula (V) into compound (VII) using a suitable alkoxylamine, aryloxylamine or hydroxylamine of general formula (VI) :



(V) (VI) (VII)

Step 4 : Transformation of the compound (VII) with an amine of general formula (VIII) or an N-hydroxyamidine of general formula (IX) thus yielding compounds (Ia) and (Ib), or transforming compound (VII) first into a nitrile (VIIa), which is then transformed into the hydroxyamidine (VIIb) that is then reacted with a carboxylic acid R^7-COOH to yield compound (Ic). :



(VII) (VIII) (Ia) (IX) (Ib) (VIIa) (VIIb) (Ic)

3. The method according to claim 1 or 2, wherein the acyl chloride of step 1 is 1'1-biphenyl-4-carbonyl chloride or 2'-methyl-1'1-biphenyl-4-carbonyl chloride.

4. The method according to any of claims 1 to 3, wherein the *oxidizing* agent of Step 2 is pyridine-sulfurtrioxide complex (Py-SO_3) in combination with DMSO.

5. The method according to any of claims 2 to 4, wherein the reaction is performed in presence of triethylamine.

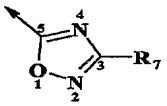
6. The method according to any of claims 1 to 5, wherein the alkoxylamine used in step 3 is O-methylhydroxylamine hydrochloride.

7. The method according to any of claims 1 to 6, wherein R_1 is a methyl group, R_2 is a biphenyl.

8. The method according to any of claims 1 to 7, wherein B is an amido group of the formula $-(C=O)NHR_5$, with R_5 being an C_1-C_6-alkyl aryl group.

9. The method according to claim 8, wherein R_5 is a phenylethyl group, which is substituted with an amino or hydroxy group.

10. The method according to any of claims 1 to 7, wherein B is a 1,2,4 oxadiazole substituent



(Xa)

(Xb)

with R_7 being a C_1-C_6-alkyl or a cycloalkyl optionally containing one or 2 hetereroatoms.

11. The method according to any of claims 1, 3, 4, or 6 to 7, wherein B is $-(CH_2)n$-X-R_8, with X being O, R_8 being hydrogen; and n being 1.

12. The method according to any of claims 1 to 11, wherein the compound is selected from the group consisting of:

(2*S*,4*E* and 4*Z*)-*N*-[(2*S*)-2-hydroxy-2-phenylethyl]-4-(methoxyimino)-1-[(2'-methyl[1,1'-biphenyl]-4-yl)carbonyl]-2-pyrrolidine carboxamide,

(3*E*,5*S*)-1-([1,1'-biphenyl]-4-ylcarbonyl)-5-[3-(2-hydroxyethyl)-1,2,4-oxadiazol-5-yl]-3-pyrrolidinone *O*-methyloxime,

(3*Z*,5*S*)-1-([1,1'-biphenyl]-4-ylcarbonyl)-5-[3-(2-hydroxyethyl)-1,2,4-oxadiazol-5-yl]-3-pyrrolidinone *O*-methyloxime,

(3*E*,5*S*)-5-[3-(2-hydroxyethyl)-1,2,4-oxadiazol-5-yl]-1-[(2'-methylbiphenyl-4-yl)carbonyl]pyrrolidin-3-one *O*-methyloxime,

(3*Z*,5*S*)-5-[3-(2-hydroxyethyl)-1,2,4-oxadiazol-5-yl]-1-[(2'-methylbiphenyl-4-yl)carbonyl]pyrrolidin-3-one *O*-methyloxime,

(3*EZ*,5*S*)-1-([1,1'-biphenyl]-4-ylcarbonyl)-5-{5-[(dimethylamino)-methyl]-1,2,4-oxadiazol-3-yl}-3-pyrrolidinone *O*-methyloxime,

(3*Z*,5*S*)-1-([1,1'-biphenyl]-4-ylcarbonyl)-5-{5-[(dimethylamino)-methyl]-1,2,4-oxadiazol-3-yl}-3-pyrrolidinone *O*-methyloxime,

(3*E*,5*S*)-1-([1,1'-biphenyl]-4-ylcarbonyl)-5-{5-[(dimethylamino)-methyl]-1,2,4-oxadiazol-3-yl}-3-pyrrolidinone *O*-methyloxime,

(3*EZ*,5*S*)-5-{5-[(dimethylamino)methyl]-1,2,4-oxadiazol-3-yl}-1-[(2'-methylbiphenyl-4-yl)carbonyl]-pyrrolidin-3-one *O*-methyloxime,

(3*Z*,5*S*)-5-{5-[(dimethylamino)methyl]-1,2,4-oxadiazol-3-yl}-1-[(2'-methylbiphenyl-4-yl)carbonyl]-pyrrolidin-3-one *O*-methyloxime,

(3*E*,5*S*)- 5-{5-[(dimethylamino)methyl]-1,2,4-oxadiazol-3-yl}-1-[(2'-methylbiphenyl-4-yl)carbonyl]-pyrrolidin-3-one *O*-methyloxime, and

(3Z/E, 5S)-1-(biphenyl-4-yl carbonyl)-5-hydroxymethyl) pyrrolidine-3-one-O-methyloxime.